Roche

Pharmaceuticals

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Nutley, August 20, 1999

Re: Docket No. 99D-0529
Draft Guidance to Industry: Changes to an Approved NDA or ANDA

Dear Sir or Madam:

Hoffmann-LaRoche supports the FDA's ongoing efforts to streamline approaches to CMC changes to New Drug Applications. In a number of respects, the SUPACs have provided regulatory relief to the pharmaceutical industry. Since the passing of FDAMA in November 1997, it has been unclear whether FDA would fulfill its obligations under the Act with a continuation of the SUPAC-type guidances, or take a bolder approach that would provide significantly greater regulatory relief. With the issuance of the subject draft guidance, the FDA has chosen the former approach. While it does provide relief in a number of areas, it appears to fall short of providing significant relief and, in fact, also appears to add to regulatory burden in a number of other areas. The categorical approach to the vast array of topics subject to CMC change guidances has resulted in a document that is confusing to follow, and at times ambiguous. In general, it also restricts flexibility, which FDA itself has always touted as an advantage of previous guidelines.

In general, it is disappointing that FDA has rejected PhRMA's 1998 decision tree approach. That approach provided a scientifically sound mechanism for defining filing requirements based upon the real impact of changes to product quality supported by actual data, rather than by defining filing requirements based upon an *a priori* approach to assessing "potential" to impact product quality. Either approach could require the same degree of investigation, data and documentation, and scientifically based conclusions. However, the decision tree approach offers the opportunity for a significantly greater degree of flexibility and relief, without compromise to safety and efficacy.

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99D-0529

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Clearly, FDA has chosen not to take the substantial step forward in redefining what changes constitute "substantial potential to adversely affect the safety or efficacy of the drug." Instead, it has relied on an historical and anecdotal collection of experiences, when a data-driven case-by-case approach would provide the regulatory relief we believe Congress intended without compromising safety or efficacy.

Nonetheless, Roche feels compelled to offer more specific input on the proposed guidance itself. This is attached.

Yours sincerely,

Hoffmann-La Roche Inc.

David Ridge, Ph.D.
Group Director
Drug Regulatory Affairs

DNR/jaw
Attachment
HLR No. 1999-2059

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Comments to FDA Guidance to Industry
Changes to an Approved NDA or ANDA

Note:

- Additions of new text appear in Italics.
- Suggested deletions appear as strikethroughs.

Sec.	Page	Line	Suggested Change	Comment
I	2	24	to ~~validate~~ *verify* or *qualify*	The use of the term "validate" as presented in FDAMA and reflected in the guidance is sure to cause confusion with cGMP process validation. It would require appropriate footnoting when referenced in print, and clarification when referenced in discussion. Clearly this problematic situation must be avoided. This pertains throughout the document.
I	2	32-34		This sentence makes it clear that, in cases of inconsistencies between this guidance and previous guidances, this guidance is to supercede all others. However, if this guidance is more vague, but supercedes more specific guidances, there is an opportunity for reviewers to rely primarily on this (more vague) guidance and consequently vary considerably in their interpretations. An obvious, yet unattractive, solution would be to update and reissue all other guidances subsequent to the issuance of this one in order to eliminate the problem.
II	3	66	. . . FDA determines *within another 30 days* that . . .	Resolution of the discrepancy should not exceed 30 days.
	3	72-3	, FDA may order the manufacturer to cease distribution . . . . (21 CFR 314.70 (c)(7) *only if safety and/or efficacy is clearly compromised.*	It must be made clear that FDA issues unrelated to safety or efficacy cannot force the manufacturer to cease distribution
IV.A.	4	105	~~Validate~~ *Qualify* the Effects of the Change	See line 24 comments above
	4	108	. . . and potency of the product *(footnote)*	It must be made clear, perhaps through a footnote, that it is not the intent of this language to always assess the impact of the change directly upon the drug product, but that the assessment can be successfully

Sec.	Page	Line	Suggested Change	Comment
				accomplished by establishing comparability at an earlier stage in the (drug substance or drug product) process
IV.A.2.	5	134	. . . effectiveness of the product *will be or* have been affected.	See lime 108 comment
	5	145	. . .impurity that is above *an ICH qualification threshold,* or a previously qualified level.	New or increased impurities below the ICH threshold need not be qualified.
IV.B.	6	154	B. ~~Equivalence~~ *Comparability*	It might be advantageous to use a term consistent with "comparability" protocols.
IV.C.	6	176	. . . and/or identification *(footnote).*	A footnote should clarify that the need to qualify and/or identify follows the ICH guidelines for such and that new or increased impurities falling below the threshold do not represent an adverse effect.
VI.A.	7	198		Footnote 7 is unclear as to whether it is intended to include sites of container/closure component fabrication as manufacturing sites. It clearly should not.
	8	213		The term "type of operation" has always demanded clarification - and still does. Clarify in glossary.
	8	213-15		This provision re. discontinuation is unacceptable as-is. Some reasonable timeframe (e.g., 5 years) needs to be allowed.
	8	215		It is assumed that the exclusion from the previous definition that sites be inspected "within the last two years" was deliberate.
	8	238		Further context related to "certain technology" needs to be provided.
VI.B.	9	247-69		References to "sites", "sites on the same campus", "sites on a different campus", etc. lead to ambiguity unless explicitly stated in each case. References to "new sites" may incorrectly imply newly constructed rather than just different sites. Sites on a "different campus" might

Sec.	Page	Line	Suggested Change	Comment
				incorrectly imply under ownership of the same company. These need to be clarified
	9	273-6		This provision for a CBE implies that the applicant itself must have previously transferred a product to that site. Why not any other applicant for that product type? The logic is unclear.
VI.C.	10	284-309		This section is confusing and ambiguous. It is likely that this entire section can be collapsed into a much simpler statement. It would perhaps also be useful to refer to "site" changes with regard to different campuses but to "facility" changes with regard to the same campus. Clarify in glossary.
VI.D.	11	313-40		It is considered inappropriate to file information re. site changes on the same campus for many of these operations when the specific location is not typically filed to the NDA and therefore should not have to be reported (e.g., secondary packaging (1.), labeling (2.), testing (3.), non-sterile processing(4. and 5.), and floor plans (7.)
	11	335-6	~~8. Improvements to manufacturing areas that provide greater assurance of quality.~~	Point 8. Is ambiguous and should be clarified or deleted.
VII.B.4.	13	408	. . . . manufacturing process or technology *for drug product* from that . . .	It is presumed that only the first two bullets in the referenced section are intended to relate to drug product (and item 5. to drug substance).
	13	413	~~Filtration to centrifugation~~	If this is intended to relate to drug substance, it is inappropriate, since synthesis descriptions generally refer to "filtration" which also allows for centrifugation.
	14	414	~~Change in the route of synthesis of a drug susbtance~~	Is inappropriate in this section and redundant to the bullet below.
	14	416	~~Any~~ *Substantial* process changes made	" Any" is too absolute and offers no flexibility in fine tuning the final intermediate process.

Hoffmann-La Roche Inc.
Comments to FDA Guidance to Industry
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Sec.	Page	Line	Suggested Change	Comment
VII.B.5.	14	418-420	Changes in the synthesis or manufacture of drug substance that ~~may~~ *significantly* affect its impurity profile and/or the physical, chemical or biological properties.	The limits of such changes are not defined. This is the perfect example of why such changes should not be categorized based on 'potential for risk' when synthesis or process changes vary drastically. Risk can be mitigated by assessment of the impact of the change and then categorized based on impact. In itself, it also makes no mention of the provision in BACPAC I for CBEs for early synthesis changes. If this guidance is to supercede all others, then those provisions for relief in BACPAC I are in question.
VII.B.7.	14	424	. . . new process for ~~reprocessing~~ *reworking* a batch	A prior approval for reprocessing violates the distinction traditionally made between reworking and reprocessing.
VII.C.	14	427-91		The attempt to be comprehensive in this guidance has caused certain BACPAC I CBE changes to be conspicuously absent here (e.g., "Changes That Do Not Involve New Starting Materials or Intermediates"). It is inconceivable that there are not more drug substance changes listed here or in 'Annual Reports'.
VII.C.1.a	14	431	~~Any~~ *Significant* changes in the process, *critical* process parameters and/or *critical* equipment, . . .	As above, "any" is absolute and provides no flexibility. Only changes to critical process information should be categorized as such. This is particularly true for drug substance process information. Therefore, "critical" process information should be defined here, and in the NDA Content and Format Guideline.
VII.D.1.	16	481-2	Changes to equipment of the same design and/*or* operating principle and/or changes in scale, *if originally defined in the NDA*, except as otherwise noted.	Same operating principle, not same design, should be key here. Equipment and scale, particularly for drug substance, is not generally reported in the NDA.
	16	491	Add: *6. Minor processing changes not affecting a critical parameter, or beyond the variations already provided for in the NDA, especially for*	There needs to be more flexibility for reporting of minor changes.

Sec.	Page	Line	Suggested Change	Comment
			APIs.	
VIII.A.	16	494-504		The definition here of "specification" is all encompassing and creates unnecessary burden on changes to "specs" for raw materials, reagents, etc. in drug substance, but also for in-process controls in drug product. A solution would be to limit the definition of "specs" to drug substance and drug product (i.e., regulatory specification), and then to designate "controls" for all the others under less regulatory burden. Also, the distinction between test and procedure needs clarification. (e.g., Would a "test" be the "Assay" and the "procedure" be "HPLC with all the details")- or - would "test" mean "HPLC" and "procedure" mean "all the details? ")?
	16-17	505-512	A regulatory ~~analytical procedure~~ *specification* is the ~~analytical procedure~~ *specification* proposed by	Since a "procedure" is only one component of a "specification", it is assumed that the suggested change is appropriate, historical convention notwithstanding. Furthermore, this paragraph uses the phrase "regulatory analytical procedure" both in the context of the NDA procedure and the USP procedure. Better clarification must be provided if the present terminology is maintained (e.g., the NDA procedure might be the regulatory analytical procedure and the USP procedure might be the compendial regulatory procedure. Consistent with the suggested change, using "regulatory specification" and "compendial specification" would be preferred, since the two could differ in any one of the three aspects (i.e., test, procedure, criteria).
VIII.B.	17	513-531		In this section and elsewhere, the use of the terms test, procedures and criteria do not always seem to conform to the definitions.

Hoffmann-La Roche Inc.
Comments to FDA Guidance to Industry
Changes to an Approved NDA or ANDA

Sec.	Page	Line	Suggested Change	Comment
VIII.B.	17	517	Relaxing an acceptance *criterion for a drug substance or drug product . . . .*	See comment for lines 494-504 above
	17	518	Deleting a ~~test~~ *specification (test, procedure or acceptance criterion) for a drug substance or drug product . . . .*	See comment for lines 513-31. For example, a test (impurities by HPLC) may still be run, but only certain acceptance criteria (e.g., impurity XYZ) deleted.
	17	519	~~Establishing a new regulatory analytical procedure~~ *Replacing a current regulatory test or procedure (for drug substance or drug product) with a new one.*	For clarification. It should not be misconstrued that implementing a new (additional) regulatory test while maintaining all others would require prior approval.
	17	520	~~Deleting a regulatory analytical procedure~~	See line 518 change and comment above.
	17	522-4	. . ~~or an analytical procedure used for testing components, packaging components, the final intermediate or starting materials~~. . . .	Analytical procedures are not required to be filed in the NDA for the referenced components.
	17	528-9	~~(2) another type of analytical procedure (e.g., titrimetric)~~	As per comment to lines 494-504 above re. definitions, it is not clear whether a change from HPLC to titration is a change in the test or the procedure.
VIII.C.1.a	17	538	Any *significant* changes in the regulatory analytical procedure.	Minor changes (e.g., fine tuning of the method conditions) must be an annual report based on the "potential to adversely impact . . ." criterion.
	18	557	Add: *e. Any change made to comply with an official compendium even it may not be consistent with previous FDA requirements and may not provide a greater level of assurance of the identity, strength, quality, purity or potency of the material being tested as the specification described in the previously approved application.*	FDA must use its influence to allow only compendial changes that do not impact safety or efficacy. When this is achieved, then changes to comply with the compendial changes are no longer Prior Approval under the qualifier of "substantial potential to have an adverse effect". This would also achieve a "level playing field" between innovator and generic companies.
VIII.C.2.a	18	558	An addition *of or* to a specification or changes in the ~~methods~~ procedures or ~~controls~~ *acceptance criteria . . . .*	Consistent with the definition of "spec".
VIII.D.1.	18	567	. . .an official compendium ~~that is consistent~~	Must be reconciled with line 557 change and comment

Hoffmann-La Roche Inc.
Comments to FDA Guidance to Industry
Changes to an Approved NDA or ANDA

Sec.	Page	Line	Suggested Change	Comment
			~~with FDA requirements~~ and that provides . . . . in the approved application.	above.
VIII.D.1	19	570	. . . material being tested as the ~~analytical procedure~~ *specification* described in the approved application	Consistent with the definition of "spec".
VIII.D.4.	19	578	A change in ~~an analytical procedure~~ *a specification* for	Consistent with the definition of "spec".
VII.D.5.	19	584	~~5. Tightening of specifications for existing reference standards . . . .~~	It seems that most NDAs for small molecules do not include the elements re. reference standards that are addressed here.
IX.B.2.	20	617	*For liquid (e.g., . . .) and semisolid (e.g., . . .),* where ink	For clarity
IX.D.	21	653		Since the glossary (definition of "package") mentions dosing cups, droppers and spoons, perhaps some discussion of adding or deleting such components to the package would be in order here.
IX.D.2.	21	661-2	A change in the size and/or shape of a container ~~containing the same number of dose units,~~ , *with or without a change in the number of dosage units* for a nonsterile solid dosage form.	It is illogical, for example, to believe that increasing the size of a bottle with no increase in pill count has any less potential for adverse effect than increasing the pill count as the bottle size increases. We would also argue that introducing physicians samples in smaller bottles represents only minimal potential for an adverse effect (i.e., Annual Report)
IX.D.4.	22	683-4 & 687	Nonsterile liquid ~~oral and topical~~ *and semisolid* dosage form products	Consistent terminology should be maintained.
IX.D.7.	23	711-713	Changes in the secondary packaging components when . . . drug product, *providing this information was previously filed to the NDA.*	Secondary packaging components not intended to provide protection are generally not filed to the NDA. See comments to lines 816-18 below.
X.B.7.	24	736-7	~~Change in the labeled storage conditions, unless exempted by regulation or guidance.~~	Changes to 'less restrictive' storage conditions with appropriate evaluation should not constitute a 'substantial potential . . . ' Changes to 'more restrictive storage conditions', including the addition of

Sec.	Page	Line	Suggested Change	Comment
				cautionary conditions, is certainly not considered to represent 'substantial potential' or a prior-approval category. It must also be made clear that implementation of uniform storage statements (USSs) is an annual report. Generally (but with USSs as an example), the provision "unless exempted by regulation or guidance" can be problematic since this draft guidance presumably references other draft guidances which may be revised from their current form.
XI.A.2.	25	776-7	Changes that may *adversely* affect product sterility assurance . . .	Improvements to sterility assurance cannot also create substantial potential of risk.
XI.A.3.	25	778	Approval of a comparability protocol . . . *or a new stability protocol.*	Self-explanatory
XI.A.4.	25	779-81	Extension of the expiration dating . . . ~~or based on pilot scale batch data.~~	If pilot scale data in sufficient for approval of the original NDA, extending dating based on these same batches does not represent a "substantial potential" for impact (i.e., prior-approval).
XI.B.	26	785	Add: *A reduction of expiration dating in order to provide assurance that the drug product will meet all quality specifications over its shelf-life.*	If the drug product's ability to meet specifications over its shelf-life is in question, increased assurance can be gained by a reduction in dating.
XI.C.2.	26	793	Addition of time points . . . *or reasonable deletion of time points after a significant body of data has been collected.*	It is reasonable to consider deleting e.g., 3, 9 and/or 18 mo. time points after significant data are available.
XI.C.3	26	794	*Reference Standards*:	This section is considered to be inappropriate for the majority of small molecule products and should be removed or qualified.
Glossary	28	836	Undergo further *physical or* molecular change before . . .	We propose that unmilled, undried, etc. API is still considered to be an intermediate.
	28	850-1	A satisfactory *current* cGMP inspection is ~~one~~ *an inspection (either cGMP or PAI)* which	We argue that a pre-approval inspection represents a cGMP inspection for that operation or dosage form. To introduce a new product to a site that has had a

Sec.	Page	Line	Suggested Change	Comment
				current PAI does not represent "substantial potential". We also assume that the omission of the "within the past two year" was unintentional. This criterion must be provided for consistent interpretation by both the agency and the applicant.
	28	816-18 and 863-4		These definitions allow for two classes of secondary packaging components: Protective and non-protective. While this guidance attempts to maintain the distinction, there is some opportunity for confusion. As the 5/99 Guidance on Container/Closure (p.16) focuses primarily on the protective aspects of secondary packaging, perhaps the term "secondary" could be reserved for protective components and nonprotective components be considered "external components" and not part of the container closure system. This might also allow for added clarity of filing/documentation requirements (i.e., external components need not be filed).
	29	870	~~Validate~~ *Verify*, or *Qualify*, or *Technically assess* . . .	As stated earlier, the term validate will only create problems that can be avoided here

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